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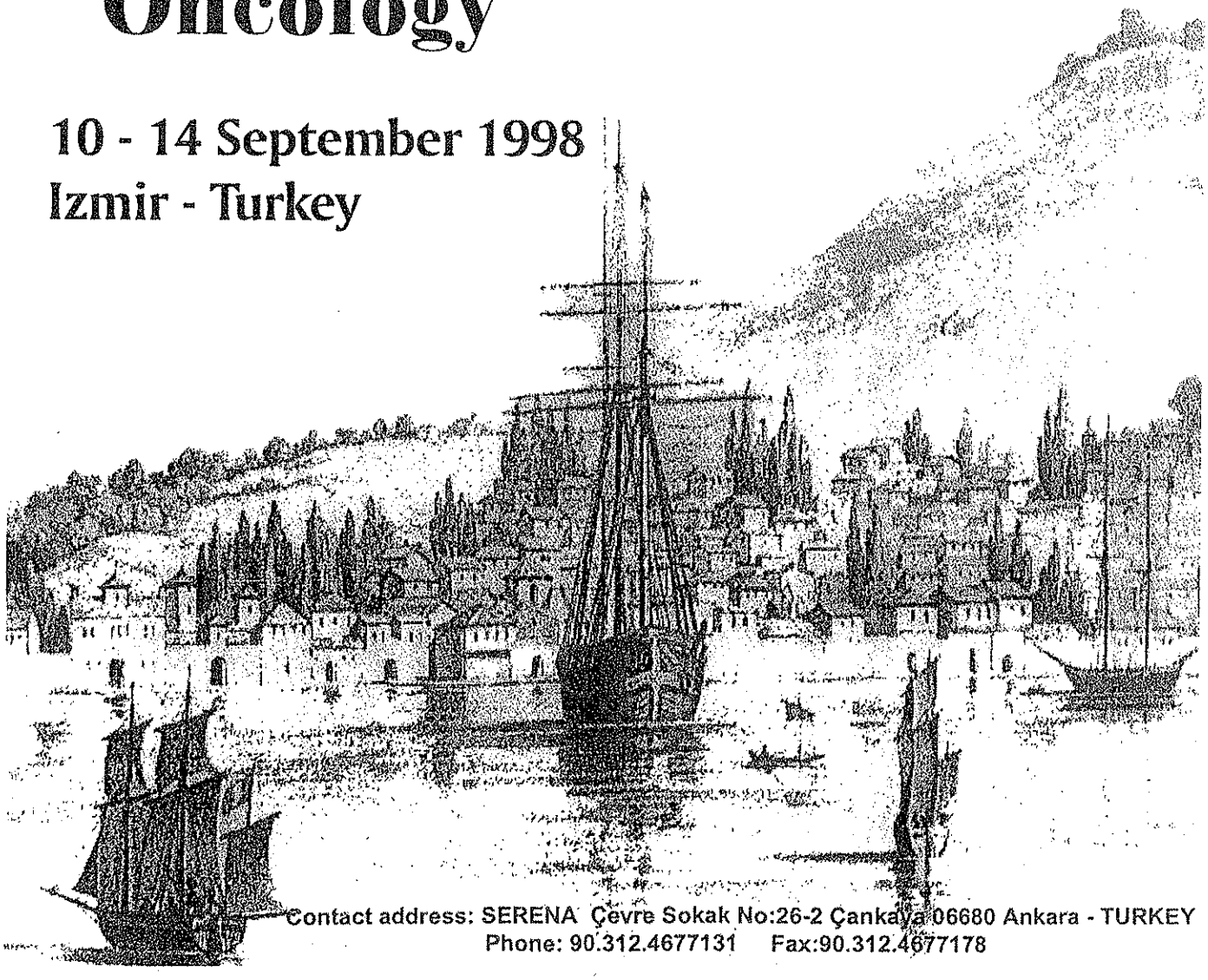

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IMPORTANCE OF *p53* MUTATIONS IN THE PROGNOSIS OF BREAST CANCER

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Mutations eliminating or altering the p53 protein function are the most common genetic alterations observed in human cancers. Cells lacking normal p53 function have a selective growth advantage and are more resistant to ionizing radiation and some anticancer drugs than cells with normal p53. Thus, cells with mutated *p53* genes might be expected to be clinically more aggressive than cells with normal *p53* genes.

This study was designed to test the hypothesis that the presence of *p53* gene mutations can be a prognostic factor in breast cancer. Mutations within exons 5, 6 and 7 of the *p53* gene were detected by using PCR-SSCP method. Forty-seven formalin fixed, paraffin embedded breast tissue samples were obtained from 23 metastatic and 24 non-metastatic breast cancer patients. The frequency of *p53* gene mutations in the PCR products of the exons 5-6 and 7 were found as 2.1 % and 8.8 %, respectively. The localization of the mutations were identified by restriction enzyme digestion. One of the samples was found to be codon 248 mutant. The frequency of p53 mutations in metastatic cases was found as 4.3 % and in non-metastatic cases as 16.7 %. It was concluded that p53 mutations can be an early event in cancer progression and can be used as a predictor of metastasis.

Although exon 7 is accepted as the hot spot region, in order to accurately estimate the importance of *p53* gene mutations on breast cancer prognosis, it is necessary to detect the region between exons 5-9 which are conserved during the evolutionary development. The clinical follow-up of the patients and the mutational detection of the gene is still in progress.

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THE ROLE OF KERATINOCYTE GROWTH FACTOR(KGF) RECEPTOR AND HEPARIN PROTEOGLYCANS (HSPGs) ON THE CELL CYCLE AND CELL SURVIVAL AFTER IONIZING RADIATION

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Keratinocyte growth factor (KGF) is a member of heparin-binding fibroblast growth factor family (FGF-7) that acts specifically on cells of epithelial origin. The biologic activity of KGF is known to be mediated via KGF receptor (KGFR) which is specific high affinity cell surface protein. Heparan sulfate proteoglycans (HSPGs) have a curicial role as a coordinator for the interaction of KGF and KGFR. In addition, KGF's high and low affinity receptors participate in signal transduction pathway as well. KGF has a potent mitogenic activity on the normal epithelial cells and has been found to enhance cell survival in irradiated mice. Heparin is also known to inhibit the mitogenic activity of KGF in cells that express the KGFR. These findings suggested that KGF, KGFR and HSPGs might be important in the cell cycle progression. To gain an insight into these hypotheses, we studied the role of KGFR and HSPGs on the cell cycle and cell survival after ionizing radiation treatment. In this study, four different CHO cell lines:" *i*-Wild type CHO cells (CHO WTC) *ii*-CHO cells tranfected with KGFR (CHO WTA) and *iii*-CHO mutant cells that were transfected with KGFR but defective in their metabolism of glycosaminoglycans (GAGs) (CHO 745 C), *iv*-CHO mutant cells that are defective in their metabolism of GAGs (CHO 745 C) " have been used. Each cell line was exposed to ionizing radiation and the percentage of cell population in each phase of the cell cycle was determined at various intervals after irradiation using flow cytometry. We established cell survival and dose relationships for each cell line and carry out comparative analyses. There were differences in terms of survival of cell lines in the presence or absence of KGFR and HSPGs. We found that KGFR and HSPGs enhance cellular capacity to survive ionizing radiation. Furthermore, cell cycle analysis shows an increase in the duration of G2 arrest. These findings suggest that KGFR and HSPGs might also have an important task in the acquisition of resistance of human tumors to radiation, and thus may be important in decision of therapy modality.

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HUMAN PAPILLOMAVIRUS (HPV) DNA IN UTERINE CERVIX DETECTED BY POLYMERASE CHAIN REACTION

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The role of HPV in the development of cervix cancer has reinforced by clinical, epidemiological and experimental data. The prevalence studies yielded a range percentiles from 40-to 100 of HPV DNA in cervical carcinoma. This differences probably due to variation in the techniques and geographical localisation. There is little known about HPV prevalence in Turkey. We investigated HPV prevalence in the uterine cervix cancer in İzmir. Formalin-fixed paraffin embedded tissues obtained from 15 patients with adenocarcinoma, 44 patients with cervical intraepithelial neoplasia (CIN), 19 patients with squamous cell carcinoma, 1 patient with mixed carcinoma, and also tissues from 22 patients without cervix cancer were examined for HPV DNA with polymerase chain reaction (PCR). We used L1 consensus (MY09/MY11) primers. HPV DNA was detected in 7 % of adenocarcinoma, 19 % of CIN1, 14 % of CIN2, 33 % of CIN3, and 33% of squamous cell carcinoma and 1/1 (100 %) of mixed carcinoma of uterine cervix. None of normal tissues was found HPV DNA. These data shown that HPV prevalence in uterine cervix cancers in our study group is lower than literature and HPV DNA is more prevalent in both squamous cell carcinoma and CIN than in adenocarcinoma.

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INSTABILITY WITHIN THE TGFβ RII GENE IN EPITHELIAL CANCERS

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Transforming growth factor beta (TGFβ) is a potent cytokine that regulates growth, differantiation, and extracellular matrix deposition in many cell types. TGFβ stimulates growth of cells of mesenchymal origin, whereas inhibits proliferation of cells of epithelial origin.

TGFβ signals by contacting two distantly related transmebrane serine/threonine kinases named receptor I (TGFβ-RI) and receptor II (TGFβ-RII). TGFβ binds directly to receptor II, which is constitutively active kinase. Bound TGFβ is then recognized by receptor I which is recurited in to the complex and becomes phosphorylated by receptor II.

The RII gene has two sites of repetitive sequances: poly(A) (nucleotides 709-718) and GT repeat (nucleotides 1931-1936). Insertion, deletions and/or frame-shift mutations result in truncated RII receptors.

We evaluated 41 cases of various types of epithelial cancer (15 with colorectal, 26 with bilateral breast cancer), for A10 frame-shift mutations. A10 mutations were not detected in any of the colorectal cancer samples. 1 out of the 26 bilateral breast cancer samples show mutations of the RII gene. It is concluded that mutations of the TGFβ-RII gene may contribute to cancer pathogenesis. But does not have a major role in epithelial carcinogenesis. To elucidate its exact contribution, extensive studies on larger patient groups should be investigated.